

Adherence to Antiretroviral Therapy in Children and Adolescents With HIV

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Panel's Recommendations
<ul style="list-style-type: none">• Strategies to maximize adherence should be discussed before and/or at initiation of antiretroviral therapy (ART) and before changing regimens (AIII).• Adherence to therapy must be assessed and promoted at each visit, and strategies to maintain and/or improve adherence must be continually explored (AIII).• In addition to viral load monitoring, at least one other method of measuring adherence to ART should be used (AIII).• Once-daily antiretroviral regimens and regimens with a low pill burden should be prescribed whenever feasible (AII*).
<p>Rating of Recommendations: A = Strong; B = Moderate; C = Optional</p> <p>Rating of Evidence: I = One or more randomized trials in children[†] with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children[†] from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children[†] with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children[†] from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion</p> <p>[†] Studies that include children or children/adolescents, but not studies limited to postpubertal adolescents</p>

Background

Adherence to antiretroviral therapy (ART) is a principal determinant of virologic suppression. Suboptimal adherence may include missed or late doses, treatment interruptions and discontinuations, and subtherapeutic or partial dosing.^{1,2} Poor adherence will result in subtherapeutic plasma antiretroviral (ARV) drug concentrations, facilitating the development of resistance to one or more drugs in a given ARV regimen and possible cross-resistance to other drugs in the same class. Multiple factors—including regimen potency, pharmacokinetics, drug interactions, viral fitness, and the genetic barrier to ARV resistance—influence the adherence–resistance relationship.^{3–5} In addition to compromising the efficacy of the current regimen, suboptimal adherence can limit the options for future effective ARV drug regimens in patients who develop multidrug-resistant HIV; it also can increase the risk of secondary transmission of drug-resistant virus.

Poor adherence to ARV drugs is commonly encountered in the treatment of children and adolescents with HIV. Medication formulation and palatability, frequency of dosing, side effects, drug toxicities and a child's age and developmental stage can affect adherence. In addition, many psychosocial, behavioral, and structural barriers for children and caregivers have also been associated with inadequate adherence. No consistent predictors of either good or poor adherence in children have been identified.^{6–8} However, findings from the U.S. Pediatric HIV/AIDS Cohort Study (PHACS) demonstrated that the prevalence of nonadherence increased with age. Among 381 children and adolescents with perinatally acquired HIV, the prevalence of nonadherence increased from 31% to 50% ($P < 0.001$), and the prevalence of unsuppressed viral loads increased from 16% to 40% ($P < 0.001$) between pre-adolescence and late adolescence/young adulthood.⁹ Similarly, in a report from the Early Pediatric Initiation Canada Cure Cohort, only 73% of the children with perinatal HIV

initiated on ART maintained viral suppression 3 years after it was first achieved.¹⁰ Furthermore, several studies have demonstrated that adherence is not static and can vary with time on treatment.¹¹ Adolescents struggle with sustained adherence over time. In a study of 933 adolescents in South Africa aged 10 to 19 years followed for a 3- to 4-year period, adherence was assessed at baseline and two subsequent times via self-report of previous week ART adherence. Thirty-seven percent of participants reported continued adherence at all three assessments. Both older age ($P = 0.007$) participants and those with horizontally acquired HIV ($P = 0.002$) were more likely to report inconsistent adherence across the three assessments¹². These findings illustrate the difficulty of maintaining high levels of adherence and underscore the need to support patients and their caregivers in developing strategies for long-term adherence to ART.

Specific Adherence Issues in Children

Adherence is a complex health behavior that is influenced by drug regimen, patient and family factors, and the patient–provider relationship.^{13,14} Despite improvements over the last several years, the availability of once-daily and single-tablet ARV regimens and palatable formulations for infants and young children are still limited. Furthermore, infants and children are dependent on others for medication administration; adult caregivers may face barriers that undermine adherence in children, including forgetting doses, changes in routine, being too busy, and child refusal.^{15,16} Caregivers also may be inadequately prepared to support their child’s adherence. In a study of communication strategies among caretakers of children with perinatally acquired HIV in rural South Africa, many caregivers used coercion and threats of grave consequences of nonadherence as a communication strategy to enforce adherence.¹⁷ Furthermore, some caregivers may place too much responsibility for managing medications on older children and adolescents before they are developmentally able to undertake such tasks.¹⁸

Adherence also may be jeopardized by social and health issues within a family (e.g., substance use, poor physical or mental health, unstable housing, poverty, violence, involvement with the criminal justice system, limited social support).^{19–22} Furthermore, children with perinatally acquired HIV and adolescents with non-perinatally acquired HIV typically enter care at different developmental stages with potentially different levels of caregiver support, which can affect adherence to ART in different ways. For adolescents transitioning from pediatric to adult care, the transition can be a vulnerable time for adherence. Such factors as changing providers, navigating the health care system as the primary medical decision-maker, and changes in insurance status and prescription access can precipitate interruptions in ART and barriers to optimal adherence. Immigrant children and families—particularly, those who have recently immigrated—may face social and cultural issues and language barriers, which can affect adherence.

Adherence Assessment and Monitoring

Providers should begin assessing potential barriers to adherence and discussing the importance of adherence with patients at initiation of ART and when changing an ARV regimen. Evaluations should assess psychosocial and behavioral factors that may influence adherence, and interventions to help decrease these barriers should be supported. Providers should ask patients about their experiences with taking medications, as well as concerns and expectations about treatment. Before beginning treatment, it is important that the patient and/or caregiver explicitly agree to the treatment plan, which should include strategies to support adherence. It is also important to alert patients and caregivers to potential adverse effects (AEs) of ARV drugs (e.g., nausea, headaches, abdominal discomfort, sleep disturbances), explain how they can be managed, and emphasize the importance of informing the clinical team if they occur.

A routine adherence assessment should be incorporated into every clinical visit. Adherence is difficult to assess accurately; different methods of assessment have yielded different results, and each approach has limitations.²³⁻²⁵ Viral load monitoring is the most useful indicator of adherence and is a routine component of monitoring individuals who are on ART (see [Plasma HIV-1 RNA \[Viral Load\] and CD4 Count Monitoring](#) in the [Adult and Adolescent Antiretroviral Guidelines](#)). It also can be used as positive reinforcement to encourage continued adherence.²⁶ In addition to viral load monitoring, providers should use at least one other method to assess adherence, such as self-report of missed doses.²⁴ Table 15 below includes common approaches to monitoring medication adherence. When assessing adherence, a nonjudgmental approach and positive rather than negative feedback can be more successful in encouraging accurate reporting related to ART adherence.²⁷

Strategies to Improve and Support Adherence

When concerns about adherence emerge, a patient should be seen and/or contacted frequently to assess adherence. Strategies to improve and support adherence should be individualized to the child and/or caregivers based on the barriers identified, developmental stage, and unique circumstances. Strategies should include simplifying the ARV drug regimen, developing treatment plans that integrate medication administration into daily routines (e.g., associating medication administration with daily activities, such as brushing teeth), and optimizing the use of social and community support services. Multifaceted approaches that include regimen-related strategies; educational, behavioral, and supportive strategies focused on children and families; and strategies that focus on health care providers may be more effective than one specific intervention. Table 16 below summarizes some of the strategies that can be used to support and improve adherence to ARV medications. The Centers for Disease Control and Prevention (CDC) offer the evidence-based [Partnership for Health – Medication Adherence](#) to HIV care providers.²⁸ A recent analysis using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC)–Adolescent model of HIV disease and treatment modeled the impact of a 12-month hypothetical adherence intervention (based on an interactive smartphone-based reminder system) among youth with HIV in the United States. Compared with the standard of care, the analysis showed that youth-targeted adherence interventions, even with modest efficacy to improve virologic suppression, could improve life expectancy, prevent onward HIV transmissions, and be cost-effective.²⁹

Regimen-Related Strategies

ARV regimens should be simplified with respect to the number of daily doses and number of pills or volume of liquid prescribed. Efforts should be made to prescribe once-daily ARV regimens and single-tablet regimens whenever feasible (see Table 18 in [Management of Children Receiving Antiretroviral Therapy](#)). Several studies in adults have demonstrated better adherence with once-daily ARV regimens than with twice-daily regimens, as well as with single-tablet formulations than with multiple-tablet regimens.³⁰⁻³⁴ See [Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class](#) and [Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents](#) for information about using FDC tablets in children. The long-acting injectable formulation of cabotegravir and rilpivirine may be an additional formulation option for patients (see [Cabotegravir](#) and [Rilpivirine](#) for eligibility criteria).

Drugs in the regimen should be chosen to minimize drug interactions and AEs (see [Management of Medication Toxicity or Intolerance](#)).³⁵ If drug-specific toxicities are thought to be contributing to nonadherence, efforts should be made to alleviate the AEs by changing the particular drug (or, if necessary, the drug regimen) when feasible. When nonadherence is related to the poor palatability of a liquid formulation or crushed pills, the offending taste can sometimes be masked with a small

amount of flavoring syrup or food if simultaneous administration of food is not contraindicated (see [Appendix A: Pediatric Antiretroviral Drug Information](#)).³⁶ Unfortunately, the taste of lopinavir/ritonavir cannot be masked with flavoring syrup. A small study of children and youth aged 4 years to 21 years found that training children to swallow pills was associated with improved adherence at 6 months post-training.³⁷

Patient/Family-Related Strategies

Patient and caregiver education is an essential component of establishing good medication adherence in children. Educating families about adherence should begin before initiating or changing ARV medications and should include a discussion of the goals of therapy, the importance of optimizing adherence, and the specific plans for supporting and maintaining a child's medication adherence. Caregiver adherence education strategies should include written and visual materials; a daily schedule illustrating times and doses of medications; and demonstration of the use of syringes, medication cups, and pill boxes. Additionally, it may be helpful to assess the medication adherence of the caregiver or other household members who currently take ARV drugs or other chronic medications. Several behavioral tools can be used to integrate taking medications into a child's daily routine. The use of behavior modification techniques, especially the application of positive reinforcements and the use of small incentives (including financial incentives) for taking medications, can be effective tools to promote adherence.³⁸

Because psychological issues and mental health disorders (e.g., depression, substance use) can affect ART adherence, recognition and treatment of these conditions is an essential part of preventing and treating nonadherence.^{39,40} The ability to talk with children about their medications is also important. If the child has not been informed of their HIV status, HIV disclosure should be discussed with the caregivers. In a recent review that explored the relationship between ART adherence and disclosure, five studies linked disclosure to improved adherence, four studies found that disclosure led to worse adherence among study participants, and five studies found no association.⁴¹ In interviews with caregivers of children with HIV in South Africa, investigators found that caregivers who had disclosed to their child that they (i.e., the child) were living with HIV were truthful in their communications and named the disease as HIV, but communication about HIV was infrequent and focused on pill taking. By comparison, those who had not disclosed used deception, deflection, and coercion in response to health-related questions and to enforce adherence.¹⁷ The decision to disclose HIV status should not necessarily be expected to improve adherence but should be based on a comprehensive assessment of psychosocial and developmental factors and the needs of the child and family.

In poorly adherent children who are at risk of disease progression and who have severe and persistent aversion to taking medications, the use of a gastrostomy tube may be considered.⁴² The growing use of telemedicine visits, which allow remote and often face-to-face interaction, provides new opportunities to support families and visualize ART handling/swallowing, as well as to conduct directly observed therapy (DOT) in the home setting. The evidence is mixed as to the efficacy of programs that are designed to improve adherence through DOT, but DOT may still be a useful strategy for some patients.⁴³⁻⁴⁵ Among 50 adolescents on atazanavir-based second-line therapy participating in a study of modified directly administered ART (mDAART), there was a significant increase in self-reported adherence (relative risk [RR] = 0.1; 95% confidence interval [CI], 0.02–0.8; $P = 0.023$) but a nonsignificant increase in virological suppression to <1,000 copies/mL ($P = 0.105$) among those randomized to the intervention arm compared to the standard of care arm.⁴⁶ A recent randomized controlled trial (RCT) of a 12-week multicomponent intervention—including remote coaching, electronic dose monitoring, and tailored outreach (Triggered Escalating Real-Time

Adherence)—for viremic youth in the United States demonstrated improved adherence but not viral suppression compared with the standard of care.²¹

Other strategies to support adherence include using mobile applications (apps) that remind patients to take medications; setting cellphone alarms to go off at medication times; sending text-message reminders; conducting motivational interviews; providing pill boxes, blister packaging, and other adherence support tools; and delivering medications to the home. The CDC has an adherence toolkit, that includes a free mobile app ([Every Dose, Every Day \(E2D2\) Toolkit and App](#)).

Several systematic reviews evaluating the use of mobile phone technologies to improve ART adherence (mHealth) have been published. In a recent review, the authors found what they described as “ambiguous results with high variability” about the effectiveness of mHealth interventions to improve adherence in low- and middle-income countries.⁴⁷ Of 17 studies, 56% reported a statistically significant positive impact of mHealth on adherence; 44% reported insignificant results. Another systematic review reported that the efficacy of mobile short message service (SMS) interventions varied depending on the specific SMS intervention tested.⁴⁸ A third systematic review of the effectiveness of using mobile phone interventions to improve adherence to ART also reported mixed results; effectiveness varied depending on the measured outcomes and the specific intervention (e.g., whether the study evaluated the use of texts or the use of phone calls).⁴⁹ It should be noted, however, that the evidence base for effective adherence interventions in adolescents and young adults who are taking daily ART is limited.⁵⁰⁻⁵⁶

Lowenthal et al. examined the association between medication-specific reactance—an aversive response to perceived threats against personal agency—and treatment failure in a cohort of adolescents with HIV in Botswana. Reactant individuals may hear health messaging as a threat to their perceived freedom and respond by engaging in the opposed behavior. Adolescents, scoring >4 on a 5-point scale had 2.05-fold (95% CI, 1.23–3.41) greater odds of treatment failure than non-reactant youth ($P = 0.043$). Psychological reactance needs further study and may provide some insight into adherence behaviors among youth; it also may be important to consider in adherence counseling and in designing interventions.⁵⁷

Two recently published studies provided evidence of the efficacy of peer-based interventions to improve ART adherence and viral suppression among adolescents and young people living with HIV in Africa. In Project YES! in Ndola, Zambia, 273 youth aged 15 to 24 years receiving HIV care in four health facilities, including a pediatric clinic, were randomly assigned to monthly meetings with youth peer mentors. At 6 months, viral suppression improved in both study arms, but among participants in care at the pediatric clinic, the rate of viral suppression increased from 37.5% to 70.5% in the intervention arm versus the comparison arm, 60.3% to 59.4% (interaction term odds ratio, 4.66; 95% CI, 1.84–11.78).⁵⁸ Mavhu et al. tested the efficacy of a peer-led differentiated service delivery intervention on HIV clinical outcomes among adolescents with HIV aged 13 to 19 years in rural Zimbabwe. Sixteen clinics were randomized to standard of care or the enhanced intervention in which adolescents were assigned a community adolescent treatment supporter; attended monthly support group; and received text messages, calls, home visits, and clinic-based counseling. Overall, 212 adolescents were recruited at intervention sites and 284 at control sites, with a median age of 15 years. At 96 weeks, among 479 adolescents with data, 52 (25%) adolescents in the intervention arm versus 97 (36%) in the control arm had viral load >1,000 copies/mL or had died (adjusted prevalence ratio 0.58; 95% CI, 0.36–0.94; $P = 0.03$). The study reported 28 deaths (17 in the intervention arm, 11 in the control arm) and 57 hospital admissions (20 in the intervention arm, 37 in the control arm). These studies demonstrate that peer-based interventions have the potential to improve adherence and health outcomes among youth with HIV.⁵⁹

In addition to clinic- and community-based programs, camp experiences can offer a source of peer support for children and youth with HIV and other chronic illnesses. Although data are limited,⁶⁰⁻⁶² many children and youth living with HIV report attendance to camp programs to be empowering and helpful to learn about adherence to daily ART regimens.

Further evidence of the efficacy of peer-support interventions for people living with HIV comes from a recent systematic review and meta-analysis, including 20 RCTs comprising 7,605 participants from nine countries. The authors found superior retention in care (RR 1.07; 95% CI, 1.02–1.12 at 12 months follow-up) and better ART adherence (RR 1.06; 95% CI, 1.01–1.10 at 3 months follow-up) but no statistically significant difference in viral suppression (RR = 1.02; 95% CI, 0.94–1.11 at 6 months follow-up) among peer-support participants.⁶³

Health Care Provider–Related Strategies

To improve and support ART adherence, providers should maintain a nonjudgmental attitude, establish trust with patients and caregivers, and identify mutually acceptable goals for care. Providers can improve adherence through their relationships with patients and families, starting at the first visit together when they obtain explicit agreement on the medication and treatment plan, as well as strategies to support adherence. Fostering a trusting relationship and engaging in open communication are particularly important. Focus groups and semi-structured interviews were conducted with adolescents and their caregivers participating in a longitudinal adherence study. Participants who self-reported high adherence but for whom electronically monitored data reflected low adherence were selected. Adolescents described hiding and discarding pills and lying about their adherence. Adolescents and parents considered negative feedback for prior poor adherence as motivation for efforts to hide current poor adherence. The authors suggest that positive feedback for truth-telling may help develop family and staff alliances in support of adherence.²⁷

Provider characteristics that have been associated with improved patient adherence in adults include consistency, willingness to give information and ask questions, technical expertise, and commitment to follow-up. Creating an environment in the health care setting that is child-centered and includes caregivers in adherence support also has been shown to improve treatment outcomes. Providing comprehensive multidisciplinary care (e.g., with nurses, case managers, pharmacists, social workers, psychiatric care providers) also may better serve more complex patient and family needs, including adherence. Provider-initiated education about viral load and counseling targeted at understanding viral load results, the health benefits of undetectable viral load, and the undetectable = untransmittable (U=U) concept are other strategies providers can use.

Table 15. Approaches for Monitoring Medication Adherence

Routine Assessment of Medication Adherence in Clinical Care ^a	Description
Monitor viral load.	Viral load monitoring should be done more frequently after initiating or changing medications. ^a
Assess a quantitative self-report of missed doses.	Ask the patient and/or caregiver about the number of missed doses over a defined period (1, 3, or 7 days).
Request a description of the medication regimen.	Ask the patient and/or caregiver about the name, appearance, and number of medications and how often the medications are taken.
Assess barriers to medication administration.	Engage the patient and caregiver in a dialogue about potential barriers to adherence and strategies to overcome them.
Monitor pharmacy refills.	Approaches include a pharmacy-based or clinic-based assessment of on-time medication refills.
Employ telemedicine to monitor and support medication administration.	Telemedicine visits allow remote and often face-to-face contact and provide new opportunities to support families; to visualize ART preparation, handling, and swallowing; and to conduct DOT in the home setting.
Conduct announced and unannounced pill counts.	Approaches include asking patients to bring medications to the clinic, conducting home visits, or providing referral to community health nursing.
Targeted Approaches to Monitoring Adherence in Special Circumstances	Description
Implement DOT in person and via telemedicine.	Include a brief period of hospitalization if indicated.
Measure drug concentration in plasma or DBS.	Measuring drug concentrations can be considered for particular drugs.
Approaches to Monitoring Medication Adherence in Research Settings	Description
Measure drug concentrations in hair.	Measuring hair drug concentrations can be considered for particular drugs; it provides a good measure of adherence over time. ^{23,64,65}
Use electronic monitoring devices.	Approaches include MEMS caps and Wisepill.
Use mobile phone-based technologies.	Approaches include interactive voice response, text messaging, and mobile apps.

^aSee [Clinical and Laboratory Monitoring of Pediatric HIV Infection](#) regarding the frequency of adherence assessment after initiating or changing therapy.

Key: apps = applications; ART = antiretroviral therapy; DBS = dried blood spots; DOT = directly observed therapy; MEMS = Medication Event Monitoring System

Table 16. Strategies to Improve Adherence to Antiretroviral Medications

Initial Intervention Strategies
<ul style="list-style-type: none"> • Establish trust and identify mutually acceptable goals for care. • Obtain explicit agreement on the need for treatment and adherence. • Determine whether the child is aware of their HIV status. Consider talking to the child's caregivers about disclosing this information to the child in a developmentally appropriate way. • Identify psychosocial, behavioral, or structural barriers that may affect adherence and help child and/or family access resources to help eliminate these barriers. • Identify family, friends, health team members, and others who can support adherence. • Educate the patient and family about the critical role of adherence in therapy outcome, including the relationship between partial adherence and resistance and the potential impact on future drug regimen choices. • With the patient and family together, develop a treatment plan that they believe is achievable. • Work with the patient and family to make specific plans for taking medications as prescribed and for supporting adherence. Assist them in arranging administration during day care, school, and in other settings, when needed. Consider home delivery of medications. • Identify barriers—such as co-pays and insurance access—related to medication access to help prevent interruptions in ART. • Schedule a home visit or telemedicine visit to review medications and determine how they will be administered in the home setting. • In certain circumstances, consider a brief period of hospitalization at the start of therapy for patient education and to assess the tolerability of the chosen medications.
Medication Strategies
<ul style="list-style-type: none"> • Choose the simplest regimen possible; reduce dosing frequency, pill size, and number of pills (see Appendix A, Table 1. Antiretrovirals Available in Fixed-Dose Combination Tablets or as a Co-packaged Formulation, by Drug Class and Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: Minimum Body Weights and Considerations for Use in Children and Adolescents). • When choosing a regimen, consider the patient's routines and potential variations in patient and family activities. • Choose the most palatable medicine possible (pharmacists may be able to add syrups or flavoring agents to improve palatability). • Choose drugs with the fewest AEs; provide anticipatory guidance for managing AEs. • Simplify food requirements for medication administration. • Prescribe drugs carefully to avoid adverse drug–drug interactions. • Assess pill-swallowing capacity and offer pill-swallowing training and aids (e.g., pill-swallowing cup, pill glide). Adjust pill size as needed. • Choose ARV regimens with high genetic barriers to resistance, when available, if there are concerns about adherence.
Follow-Up Intervention Strategies
<ul style="list-style-type: none"> • Members of the multidisciplinary team should monitor adherence at each visit. In between visits, adherence can be monitored and supported by telephone, email, text, and other secure applications; confidentiality of any communication approach must be ensured. • Provide ongoing support, encouragement, and understanding of the difficulties associated with maintaining adherence to daily medication regimens.

- Provide education and counseling that explain the meaning and significance of viral load results.
- Use patient education aids, including pictures, calendars, and stickers.
- Encourage the use of pill boxes, reminders, mobile apps, alarms, and resources such as the CDC's [Every Dose, Every Day \(E2D2\) Toolkit and App](#).
- Provide follow-up clinic visits, telephone calls, text messages, and telemedicine visits to support and assess adherence.
- Provide access to support groups, peer groups, **summer camp programs, or** one-on-one counseling for caregivers and patients.
- **Provide referrals and support access to counseling and treatment services for individuals with identified mental health problems, including depression and substance abuse.**
- Provide pharmacist-based adherence support, such as medication education and counseling, blister packs, refill reminders, automatic refills, and home delivery of medications.
- Consider DOT at home, in the clinic, or, in certain circumstances, during a brief period of inpatient hospitalization.
- Consider gastrostomy tube use in certain circumstances.
- Information on other interventions to consider can be found at the [Complete Listing of Medication Adherence Evidence-Based Behavioral Interventions](#) on the CDC's website.

Key: apps = applications; AE = adverse effect; ARV = antiretroviral; CDC = Centers for Disease Control and Prevention; DOT = directly observed therapy

References

1. Vreeman RC, Nyandiko WM, Liu H, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. *J Int AIDS Soc*. 2014;17:19227. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25427633>.
2. Hawkins A, Evangeli M, Sturgeon K, Le Prevost M, Judd A, Aalphi Steering Committee. Episodic medication adherence in adolescents and young adults with perinatally acquired HIV: a within-participants approach. *AIDS Care*. 2016;28 Suppl 1:68-75. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26886514>.
3. Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. *AIDS*. 2009;23(9):1035-1046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19381075>.
4. Judd A, Melvin D, Thompson LC, et al. Factors associated with nonadherence to antiretroviral therapy among young people living with perinatally acquired HIV in England. *J Assoc Nurses AIDS Care*. 2020;31(5):574-586. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32467489>.
5. Parienti JJ, Fournier AL, Cotte L, et al. Forgiveness of dolutegravir-based triple therapy compared with older antiretroviral regimens: a prospective multicenter cohort of adherence patterns and HIV-RNA replication. *Open Forum Infect Dis*. 2021;8(7):ofab316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34307726>.
6. MacDonell KK, Jacques-Tiura AJ, Naar S, Fernandez MI, Team ATNP. Predictors of self-reported adherence to antiretroviral medication in a multisite study of ethnic and racial minority HIV-positive youth. *J Pediatr Psychol*. 2016;41(4):419-428. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26498724>.
7. Gray ME, Nieburg P, Dillingham R. Pediatric human immunodeficiency virus continuum of care: a concise review of evidence-based practice. *Pediatr Clin North Am*. 2017;64(4):879-891. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28734516>.
8. Schlatter AF, Deathe AR, Vreeman RC. The need for pediatric formulations to treat children with HIV. *AIDS Res Treat*. 2016;2016:1654938. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27413548>.
9. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among U.S. youth with perinatally acquired HIV. *AIDS*. 2019;33(12):1923-1934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31274538>.
10. Kakkar F, Lee T, Hawkes MT, et al. Challenges to achieving and maintaining viral suppression among children living with HIV. *AIDS*. 2020;34(5):687-697. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31794519>.
11. Giannattasio A, Albano F, Giacomet V, Guarino A. The changing pattern of adherence to antiretroviral therapy assessed at two time points, 12 months apart, in a cohort of HIV-

- infected children. *Expert Opin Pharmacother*. 2009;10(17):2773-2778. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19929700>.
12. Zhou S, Cluver L, Shenderovich Y, Toska E. Uncovering ART adherence inconsistencies: An assessment of sustained adherence among adolescents in South Africa. *J Int AIDS Soc*. 2021;24(10):e25832. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34708912>.
 13. Haberer J, Mellins C. Pediatric adherence to HIV antiretroviral therapy. *Curr HIV/AIDS Rep*. 2009;6(4):194-200. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19849962>.
 14. Shubber Z, Mills EJ, Nachega JB, et al. Patient-reported barriers to adherence to antiretroviral therapy: a systematic review and meta-analysis. *PLoS Med*. 2016;13(11):e1002183. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27898679>.
 15. Marhefka SL, Koenig LJ, Allison S, et al. Family experiences with pediatric antiretroviral therapy: responsibilities, barriers, and strategies for remembering medications. *AIDS Patient Care STDS*. 2008;22(8):637-647. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18627275>.
 16. Skovdal M, Campbell C, Madanhire C, Nyamukapa C, Gregson S. Challenges faced by elderly guardians in sustaining the adherence to antiretroviral therapy in HIV-infected children in Zimbabwe. *AIDS Care*. 2011;23(8):957-964. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21400306>.
 17. Molokwane M, Madiba S. Truth, deception, and coercion; communication strategies used by caregivers of children with perinatally acquired HIV during the pre-disclosure and post-disclosure period in rural communities in South Africa. *Glob Pediatr Health*. 2021;8:2333794X211022269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34104705>.
 18. Naar-King S, Montepiedra G, Nichols S, et al. Allocation of family responsibility for illness management in pediatric HIV. *J Pediatr Psychol*. 2009;34(2):187-194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18586756>.
 19. Cluver LD, Hodes RJ, Toska E, et al. ‘HIV is like a tsotsi. ARVs are your guns’: associations between HIV-disclosure and adherence to antiretroviral treatment among adolescents in South Africa. *AIDS*. 2015;29 Suppl 1:S57-65. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26049539>.
 20. Cluver L, Meinck F, Toska E, Orkin FM, Hodes R, Sherr L. Multitype violence exposures and adolescent antiretroviral nonadherence in South Africa. *AIDS*. 2018;32(8):975-983. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29547438>.
 21. Amico KR, Crawford J, Ubong I, et al. Correlates of high HIV viral load and antiretroviral therapy adherence among viremic youth in the United States enrolled in an adherence improvement intervention. *AIDS Patient Care STDS*. 2021;35(5):145-157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33960843>.

22. Haas AD, Technau KG, Pahad S, et al. Mental health, substance use and viral suppression in adolescents receiving ART at a paediatric HIV clinic in South Africa. *J Int AIDS Soc.* 2020;23(12):e25644. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33283916>.
23. Pintye J, Bacchetti P, Teeraananchai S, et al. Brief report: lopinavir hair concentrations are the strongest predictor of viremia in HIV-infected Asian children and adolescents on second-line antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2017;76(4):367-371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28825944>.
24. Al-Hassany L, Kloosterboer SM, Dierckx B, Koch BC. Assessing methods of measuring medication adherence in chronically ill children-a narrative review. *Patient Prefer Adherence.* 2019;13:1175-1189. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31413546>.
25. Craker L, Tarantino N, Whiteley L, Brown L. Measuring antiretroviral adherence among young people living with HIV: observations from a real-time monitoring device versus self-report. *AIDS Behav.* 2019;23(8):2138-2145. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30888573>.
26. Bonner K, Mezocho A, Roberts T, Ford N, Cohn J. Viral load monitoring as a tool to reinforce adherence: a systematic review. *J Acquir Immune Defic Syndr.* 2013;64(1):74-78. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23774877>.
27. Lowenthal ED, Ohrenshall R, Moshashane N, et al. Reasons for discordance between antiretroviral adherence measures in adolescents. *AIDS Care.* 2021:1-9. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34424796>.
28. Centers for Disease Control and Prevention. Medication adherence. 2014. Available at: <https://www.cdc.gov/hiv/effective-interventions/treat/pfh-ma/index.html>.
29. Neilan AM, Bangs AC, Hudgens M, et al. Modeling adherence interventions among youth with HIV in the United States: clinical and economic projections. *AIDS Behav.* 2021;25(9):2973-2984. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33547993>.
30. Nachega JB, Parienti JJ, Uthman OA, et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis.* 2014;58(9):1297-1307. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24457345>.
31. Clay PG, Nag S, Graham CM, Narayanan S. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine (Baltimore).* 2015;94(42):e1677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26496277>.
32. Pantuzza LL, Ceccato M, Silveira MR, Junqueira LMR, Reis AMM. Association between medication regimen complexity and pharmacotherapy adherence: a systematic review. *Eur J Clin Pharmacol.* 2017;73(11):1475-1489. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28779460>.

33. Griffith DC, Farmer C, Gebo KA, et al. Uptake and virological outcomes of single-versus multi-tablet antiretroviral regimens among treatment-naïve youth in the HIV Research Network. *HIV Med.* 2019;20(2):169-174. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30561888>.
34. Altice F, Evuarherhe O, Shina S, Carter G, Beaubrun AC. Adherence to HIV treatment regimens: systematic literature review and meta-analysis. *Patient Prefer Adherence.* 2019;13:475-490. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31040651>.
35. Pham PA. Antiretroviral adherence and pharmacokinetics: review of their roles in sustained virologic suppression. *AIDS Patient Care STDS.* 2009;23(10):803-807. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19795999>.
36. Czyzewski D, Runyan D, Lopez M, et al. Teaching and maintaining pill swallowing in HIV-infected children. *The AIDS Reader.* 2000;10(2):88-94. Available at: <https://www.scinapse.io/papers/2972005888>.
37. Garvie PA, Lensing S, Rai SN. Efficacy of a pill-swallowing training intervention to improve antiretroviral medication adherence in pediatric patients with HIV/AIDS. *Pediatrics.* 2007;119(4):e893-899. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17353298>.
38. Foster C, McDonald S, Frize G, Ayers S, Fidler S. "Payment by results"--financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: a pilot program. *AIDS Patient Care STDS.* 2014;28(1):28-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24428797>.
39. Sin NL, DiMatteo MR. Depression treatment enhances adherence to antiretroviral therapy: a meta-analysis. *Ann Behav Med.* 2014;47(3):259-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24234601>.
40. Bucek A, Leu CS, Benson S, et al. Psychiatric disorders, antiretroviral medication adherence and viremia in a cohort of perinatally HIV-infected adolescents and young adults. *Pediatr Infect Dis J.* 2018;37(7):673-677. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29227462>.
41. Nichols J, Steinmetz A, Paintsil E. Impact of HIV-status disclosure on adherence to antiretroviral therapy among HIV-infected children in resource-limited settings: a systematic review. *AIDS Behav.* 2017;21(1):59-69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27395433>.
42. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics.* 2000;105(6):E80. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10835093>.
43. Bain-Brickley D, Butler LM, Kennedy GE, Rutherford GW. Interventions to improve adherence to antiretroviral therapy in children with HIV infection. *Cochrane Database Syst Rev.* 2011;12(12):CD009513. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22161452>.

44. Gaur AH, Belzer M, Britto P, et al. Directly observed therapy (DOT) for nonadherent HIV-infected youth: lessons learned, challenges ahead. *AIDS Res Hum Retroviruses*. 2010;26(9):947-953. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20707731>.
45. Hart JE, Jeon CY, Ivers LC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. *J Acquir Immune Defic Syndr*. 2010;54(2):167-179. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20375848>.
46. Chawana TD, Katzenstein D, Nathoo K, Ngara B, Nhachi CFB. Evaluating an enhanced adherence intervention among HIV positive adolescents failing atazanavir/ritonavir-based second line antiretroviral treatment at a public health clinic. *J AIDS HIV Res*. 2017;9(1):17-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31649827>.
47. Demena BA, Artavia-Mora L, Ouedraogo D, Thiombiano BA, Wagner N. A systematic review of mobile phone interventions (SMS/IVR/calls) to improve adherence and retention to antiretroviral treatment in low-and middle-income countries. *AIDS Patient Care STDS*. 2020;34(2):59-71. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32049555>.
48. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: A systematic review and meta-analysis. *PLoS One*. 2018;13(9):e0204091. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30240417>.
49. Shah R, Watson J, Free C. A systematic review and meta-analysis in the effectiveness of mobile phone interventions used to improve adherence to antiretroviral therapy in HIV infection. *BMC Public Health*. 2019;19(1):915. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31288772>.
50. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13–24 years of age: a review of the evidence base. *J Acquir Immune Defic Syndr*. 2016;72(4):387-399. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26959190>.
51. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: moving on up. *Curr Opin HIV AIDS*. 2016;11(5):477-486. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27272537>.
52. MacPherson P, Munthali C, Ferguson J, et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. *Trop Med Int Health*. 2015;20(8):1015-1032. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25877007>.
53. Kanters S, Park JJ, Chan K, et al. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV*. 2017;4(1):e31-e40. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27863996>.

54. Camacho-Gonzalez AF, Gillespie SE, Thomas-Seaton L, et al. The Metropolitan Atlanta community adolescent rapid testing initiative study: closing the gaps in HIV care among youth in Atlanta, Georgia, USA. *AIDS*. 2017;31 Suppl 3:S267-S275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28665885>.
55. Casale M, Carlqvist A, Cluver L. Recent interventions to improve retention in HIV care and adherence to antiretroviral treatment among adolescents and youth: a systematic review. *AIDS Patient Care STDS*. 2019;33(6):237-252. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31166783>.
56. Abiodun O, Ladi-Akinyemi B, Olu-Abiodun O, et al. A single-blind, parallel design RCT to assess the effectiveness of SMS reminders in improving ART adherence among adolescents living with HIV (STARTA trial). *J Adolesc Health*. 2021;68(4):728-736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/33342719>.
57. Lowenthal E, Matesva M, Marukutira T, et al. Psychological reactance is a novel risk factor for adolescent antiretroviral treatment failure. *AIDS Behav*. 2021;25(5):1474-1479. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32754779>.
58. Denison JA, Burke VM, Miti S, et al. Correction: project YES! youth engaging for success: a randomized controlled trial assessing the impact of a clinic-based peer mentoring program on viral suppression, adherence and internalized stigma among HIV-positive youth (15–24 years) in Ndola, Zambia. *PLoS One*. 2020;15(4):e0232488. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32324830>.
59. Mavhu W, Willis N, Mufuka J, et al. Effect of a differentiated service delivery model on virological failure in adolescents with HIV in Zimbabwe (Zvandiri): a cluster-randomised controlled trial. *Lancet Glob Health*. 2020;8(2):e264-e275. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31924539>.
60. Ness TE, Agrawal V, Guffey D, et al. Impact of using creative arts programming to support HIV treatment in adolescents and young adults in Eswatini. *AIDS Res Ther*. 2021;18(1):100. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34930371>.
61. Gillard A, Witt PA, Watts CE. Outcomes and processes at a camp for youth with HIV/AIDS. *Qual Health Res*. 2011;21(11):1508-1526. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21709127>.
62. Evangeli M, Lut I, Ely A. A longitudinal evaluation of an intensive residential intervention (camp) for 12–16 year olds living with HIV in the UK: evidence of psychological change maintained at six month follow-up. *AIDS Care*. 2019;31(1):85-89. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30045639>.
63. Berg RC, Page S, Ogard-Repal A. The effectiveness of peer-support for people living with HIV: a systematic review and meta-analysis. *PLoS One*. 2021;16(6):e0252623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/34138897>.
64. Olds PK, Kiwanuka JP, Nansera D, et al. Assessment of HIV antiretroviral therapy adherence by measuring drug concentrations in hair among children in rural Uganda.

- AIDS Care*. 2015;27(3):327-332. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/25483955>.
65. Chawana TD, Gandhi M, Nathoo K, et al. Defining a cutoff for atazanavir in hair samples associated with virological failure among adolescents failing second-line antiretroviral treatment. *J Acquir Immune Defic Syndr*. 2017;76(1):55-59. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/28520618>.